Biology of Learning and Memory
What is your “self?”

Your memory of your past experiences, friends and relatives, goals.

Memory is critical for our sense of who we are.

What is memory? How do we learn?
Learning

• One form of learning is classical conditioning, discovered by Ivan Pavlov in St. Petersburg.
  – He was trying to show that saliva contains enzymes that break down carbohydrates.
  – He inserted tubes into the salivary ducts of dogs and then fed them meat powder to make them salivate.
  – He noticed that after several days, the dogs salivated as soon as he walked into the room.
  – He decided to study that type of learning.
Classical conditioning

At first
- Conditioned stimulus (CS)
- Followed by
  - Food

Unconditioned stimulus (UCS)
Automatically elicits
Unconditioned response (UCR)

After some number of repetitions
- Conditioned stimulus (CS)
- Conditioned response (CR)
- Salivation

(a) Classical conditioning
Learning

• Another type of learning is operant conditioning.
• In **operant conditioning**, responses are followed by reinforcement or punishment that either strengthens or weakens a behavior.
  – **Reinforcers** increase the probability of the response.
  – **Punishments** decrease the probability of the response.
Operant conditioning

- Response: Rat enters one arm of the maze
- Reinforcement
- Punishment
- Shock
- Froot Loops
- Increased probability of same response
- Shift to different response
Some learning is neither classical nor operant:

- Male songbirds learn their father’s song, without any reinforcement. The following year they produce it, again without reinforcement.
- Females also learn to recognize the song and choose mates that sing like their father.
Biological basis of learning

• So, what changes in the brain when someone learns something?
• Pavlov believed that classical conditioning strengthened neural connections between the CS center and UCS center in the brain.
• Karl Lashley set out to prove this by searching for such engrams, or physical representations of what had been learned.
  – He believed that a knife cut should abolish the newly learned response.
Karl Lashley: Let’s test Pavlov’s hypothesis!!

If Lashley is correct, cuts between the area that processes the CS and the area that processes the UCS should disrupt the conditioning.

However, Lashley used operant conditioning: maze learning in rats.
So, Lashley made many cuts through the cortex after rats learned a maze. What did he find???
No cut made any difference in the rat’s ability to remember mazes or a brightness discrimination task.

• Why???
• Learning and memory do not depend on connections across the cortex
• Also, learning does not depend on a single area of the cortex.
  – Maze learning and visual discrimination are complex tasks. They require multiple areas.
• 2 unnecessary assumptions:
  – The cerebral cortex is the best or only place to look for an engram.
  – All kinds of memory are physiologically the same.
Karl Lashley

- Lashley proposed that:
  - All parts of the cortex contribute equally to complex behaviors like learning.
  - The cortex works as a whole, not as single isolated units.
Donald Hebb

- Hebb (1949) proposed that there are two types of memory:
  - **Short-term memory** (STM) – memory of events that have just occurred.
  - **Long-term memory** (LTM) – memory of events from previous times.
Donald Hebb

- STM compared to LTM:
  - STM has limited capacity.
    - Lets you remember a phone number long enough to call it.
    - LTM is not; you can remember many facts and experiences.
  - STM fades quickly without rehearsal.
    - It is hard to remember the phone number 5 minutes later.
    - LTM persists without constant rehearsal.
  - LTM can be called up with a cue or hint, but cues do not help us remember lost STMs.
Working Memory

• The distinction between STM and LTM has been weakened.
  – Some memories are not clearly short-term or long-term:
    • Where you parked the car this morning.
    • What you had for dinner last night.
    • These are too long ago to be STM, but you didn’t rehearse it, and it will fade over hours, days, or weeks.
• Working Memory
  – It is temporary storage of information while we actively attend to it or work on it.

• A test of working memory is the delayed response task. It requires that you respond to a stimulus that you heard or saw a short time earlier.
  • Increased activity in the prefrontal cortex during the delay helps store the memory.
  • The stronger the neural activation, the better the performance.
Delayed response task

Monkey lifts sample object to get food.

Food is under the new object.
Working memory

• Older people often have impairments in working memory.
• Declining activity of the prefrontal cortex in the elderly is associated with decreasing memory.
• Some older people are not impaired.
  – They have increased activity in prefrontal cortex, compared to younger people.
  – This may compensate for deficits in other parts of the brain.
Long-term memory has a huge capacity, but can be altered.

Alexander Luria’s patient: Couldn’t forget!!

He was asked to remember a list of words.

A year later he could recall all but two.

When told he was missing two words, he thought a bit and then came up with them.

How did he do it?
Long term memory

He had pictured the front of a house and visualized each word at a place on the house.

The two words that he missed had been placed in the shadows beneath two bushes.

When he looked more carefully, he could “see” them!
• James McGaugh’s patient A.J. has a similar problem. She is burdened by nonstop, uncontrollable memories.
• She was asked, for the past 10 years, what day of the month was Easter? She got them all correct & remembered what she did on each day!
• Typical college student knows about 50,000 words + rules of language, familiar phrases.
• Learning a language requires about 100,000 items of knowledge!!
Long term memory

• Would you like to have such ability to remember?

• These people felt it was a burden. It would be difficult to abstract and see whole patterns.

• We still do not understand what is different about their brains.
The hippocampus and amnesia

- **Patient H.M.**: his hippocampus was removed to prevent his many epileptic seizures.
- Afterwards, he had great difficulty forming new long term memories.
- Many years after the surgery, he still thought that President Truman was President of the United States.
The hippocampus and amnesia

• His short-term or working memory remained intact.
  – One task: Remember 584 for 15 minutes.
  – “Easy: Remember 8. 5 + 8 + 4 = 17. You remember 8 & subtract it from 17 and that leaves 9. Divide 9 in half and you get 5 & 4. There you are: 584. Easy.”
  – A moment later, after shifting his attention, he couldn’t remember the number or even trying to remember it.
Location of the hippocampus

(a) Corpus callosum
Thalamus
Olfactory bulb
Olfactory tract
Mamillary body
Left temporal lobe
Hippocampus

(b) Cerebral cortex
Horizontal section through left posterior cerebral cortex
Thalamus
Hippocampus

© 2007 Thomson Higher Education

Fig. 13-5ab, p. 391
The hippocampus and amnesia

• There are two major types of amnesia:
  • Anterograde ("going forward") amnesia – inability to form new memories after the brain damage occurred.
  • Retrograde ("going backward") amnesia – loss of memory for events before the brain damage.
• HM has massive anterograde amnesia after the surgery.
• There are two major kinds of memory.
• Patient HM had difficulty with declarative memory.
  – **Declarative memory**: ability to put a memory into words.
• Patient HM’s procedural memory remained intact.
  – **Procedural memory**: ability to develop motor skills (remembering or learning how to do things).
What are these 2 objects?
What are these 2 objects?
What are these 2 objects?
What are these 2 objects?
HM improves on this task, but doesn’t remember having done it.
(An example of procedural memory)
Another example of procedural learning

Procedural memory:
HM improved over 3 days, but did not remember doing it.
(b) Performance of H.M. on mirror-tracing task

Errors per trial

Day 1

Day 2

Day 3
Two Main Kinds of Memory: Declarative and procedural

Long-term memory

Declarative: Things you know that you can tell others

Nondeclarative (procedural): Things you know that you can show by doing

H.M. can’t form new declarative memories. But he can form new procedural memories.
The hippocampus and memory

• Does hippocampus size matter? There are conflicting results.
• For children, adolescents, & young adults: a smaller hippocampus is associated with better memory performance.
  – Hypothesis: cell death gets rid of neurons that are less useful.
• Older adults: some studies suggest that smaller is better; in others, larger is better.
• Hippocampus activity is more associated with memory performance than is the size.
So, what **does** the hippocampus do?

It is critical for **declarative memory**.

Example: remembering what you ate for dinner last night, or rats learning which arm of a maze contains food.

It is especially important for **spatial memory**.

Neurons respond when the animal is in a particular location.

London taxi drivers have larger than average posterior hippocampi.

That area is active when they are figuring a path from one building to another across town.
Morris water maze: Rats with hippocampal damage can eventually learn to find the submerged platform if they start from the same place, but not if they start from variable places.
Hippocampus and memory

• Evidence suggests that the hippocampus is important for “consolidation” of memories.

• **Consolidation:** the process of strengthening short-term memories into long-term memories.
  – **Theta waves** (7-10 Hz, or cycles per second) occur in hippocampus during active learning.

• Hippocampus damage impairs recent learning more than older learning.
  – The more consolidated a memory becomes, the less it depends on the hippocampus.
Hippocampus and memory

- **Reverberating circuits** of neuronal activity may contribute to consolidation.
  - Theta waves from the hippocampus may continue to activate circuits throughout the brain until biochemical changes occur.
A hypothetical reverberating circuit

Incoming axon
• Consolidation is influenced by emotions.
  – Moderate amounts of cortisol (a stress hormone from the adrenal gland), epinephrine (adrenaline), and the transmitter norepinephrine activate the amygdala and hippocampus. This enhances consolidation of recent experiences.

• It helps you remember emotion-filled events.
  – But prolonged stress impairs memory and kills hippocampal cells. (There will be more about this in a later lecture.)
Amnesia and Brain Functioning

• Different kinds of brain damage result in different types of amnesia.
• Two common types of brain damage result in:
  1. Korsakoff’s syndrome
  2. Alzheimer’s disease
• **Korsakoff’s syndrome** – prolonged thiamine (vitamin B1) deficiency impairs the brain’s ability to metabolize glucose.

• This leads to the loss or shrinkage of neurons in the brain.

• It is often due to chronic alcoholism.

• Symptoms include apathy (not caring), confusion, and forgetting.
• Alzheimer’s disease results in progressive loss of memory in old age.
• It affects 50% of people over 85.
• An early-onset form of the disease is influenced by genes, but 99% of cases are late onset.
  • Chromosome 21 contains one gene associated with Alzheimer’s disease.
  • Genes on other chromosomes may also contribute.
• About half of all patients with late onset have no known relative with the disease.
Progressive shrinking of neurons in Alzheimer’s disease
• Alzheimer’s disease is caused by an accumulation and clumping of brain proteins.
  • **Amyloid beta protein** produces widespread cell death in the cerebral cortex, hippocampus and other areas.
  • An abnormal form of the **tau** protein, part of the intracellular support system of neurons, may also contribute.
• Accumulation of the **amyloid beta** protein results in:
  – **Plaques** – *extracellular* structures formed from dying neurons.
• Accumulation of **tau** protein results in:
  – **Tangles** – structures formed from degenerating structures *within* a cell body.
Intracellular tangles of Tau proteins
Loss of brain tissue in Alzheimer’s disease
Possible treatments for Alzheimer’s disease

- A major area of damage is the basal forebrain, which contains the transmitter **acetylcholine**. One treatment is a drug that decreases breakdown of **acetylcholine**.
- **Antioxidants** block amyloid-beta production.
- Research with mice suggests the possibility of immunizing against Alzheimer’s by stimulating the production of **antibodies** against **amyloid beta** protein.
So, how do we store information in the nervous system?

- Activity in the brain results in physical changes.
- Patterns of activity leave a path of physical changes.
- Not every change is a specific memory as was once originally believed.
Storing Information in the Nervous System

- Successful stimulation of a cell by an axon leads to the increased ability of that axon to stimulate that cell in the future.
  - Simultaneous activity in the presynaptic and postsynaptic neurons is necessary.

- Long-Term Potentiation (LTP) occurs when one or more axons rapidly stimulate a dendrite.
  - This leaves the synapse “potentiated” (stronger) for a period of time, and the neuron is more responsive.
Only synapses that have been highly active become strengthened. Simultaneous stimulation by two or more axons produces LTP more strongly than repeated stimulation by a single axon. Pairing a weak input with a strong input enhances later responses to the weak input.
• Long-term depression (LTD) is a prolonged decrease in response at a synapse when axons were active at a low frequency.
  – The opposite of LTP
• Biochemical mechanisms of LTP depend on changes in glutamate synapses mostly in the postsynaptic neuron.
• Glutamate is the main excitatory transmitter.
• Rapid stimulation of two kinds of glutamate receptor results in more receptors being produced and sent to the synapse. Also, more synapses may be formed. (Don’t worry about the details.)
Before LTP

Axon releases glutamate

Glutamate molecule attached to receptor

AMPA receptor

NMDA receptor (Nothing enters usually)

Magnesium ion blocking channel

Na⁺ enters

Dendrite

© 2007 Thomson Higher Education
After LTP: additional postsynaptic receptors
• Dendrites may also form new branches.
• These changes increase the later responsiveness of the dendrite to incoming glutamate.
• Changes in presynaptic neuron can also lead to LTP.

• Extensive stimulation of a postsynaptic cell causes the release of a retrograde transmitter that travels back to the presynaptic cell to cause:
  – Increase in transmitter release.
  – Expansion of the axons.
  – Transmitter release from additional sites.
After LTP: additional presynaptic axon terminal

Axon releases glutamate repeatedly

Displaced magnesium molecule

Mg^{++}

AMPA receptor

Much Na^{+} enters

NMDA receptor

Na^{+} and Ca^{++} enter

Dendrite, much depolarized

© 2007 Thomson Higher Education
Both axon terminals and dendrites increase after repeated activity.
• Understanding the changes that enhance or impair LTP may lead to drugs that improve memory.
  – Example: Mice with genes that cause abnormal glutamate receptors learn slowly. Mice with extra genes for those receptors learn faster.
Summary

• Classical conditioning: Pairing of 2 stimuli leads to changes in the response to one of them.
  – CS + UCS $\rightarrow$ UCR (repeat many times)
  – CS $\rightarrow$ CR

• Operant conditioning: an individual’s response is followed by a reinforcer or punishment, which changes the later probability of the response.

• Pavlov thought that learning depends on the growth of a connection between 2 brain areas. Lashley showed that learning does not depend on new connections across the cerebral cortex.
Summary

• Short-term memory holds only a small amount of information and retains it only briefly, unless it is constantly rehearsed. Long-term memory retains vast amounts of material indefinitely, but recalling this information sometimes requires great effort.
Summary

• Working memory, a modern alternative to the concept of short-term memory, stores information that one is currently using. The prefrontal cortex and other areas store working memories through repetitive cellular activity.

• Impairment of memory in old age is probably due to impairments of the prefrontal cortex.
Summary

• People like H.M. with damage to the hippocampus have great trouble forming new long-term declarative memories, although they can still recall events from before the damage and can still form new procedural memories.

• The hippocampus is critical for consolidating some forms of memory but not all. It is especially important for declarative memory and spatial memory.
Summary

• Consolidation is increased by emotional arousal. Arousing events increase release of epinephrine and cortisol, which directly or indirectly stimulate the amygdala and hippocampus.

• Patients with Korsakoff’s syndrome or other types of prefrontal damage have impairments of memory. They often make up information to fill in their memory gaps, which they then remember as if they were true. Korsakoff’s results from a lack of thiamine (vitamin B1), often as a result of getting most calories from alcohol.
Summary

• Alzheimer’s disease is a progressive impairment of memory and attention disease, most common in old age. It is caused partly by the amyloid-beta protein forming plaques (clumps) in the spaces between neurons. These are formed from degenerating axons and dendrites. Tau protein forms tangles inside of neurons.
Summary

• Synapses are strengthened if they are rapidly and repeatedly activated.
• Long-term potentiation (LTP) is an increase in responsiveness at certain synapses. It is caused by brief but intense series of stimuli delivered to a neuron. LTP occurs in many brain areas and is particularly prominent in the hippocampus.
Summary

• Mechanism of LTP: Repeated excitation of one type of glutamate receptors results in the delivery of additional receptors to the synapse. Also, axons and dendrites form new branches.
• If axons are active at a very slow rate, their synapses may decrease in responsiveness—a process known as long-term depression (LTD).
• Procedures that affect LTP and LTD have similar effects on learning, suggesting that this research may lead to drugs that can help improve memory.
Practical applications

• Memory may be increased by emotional events, which result in increased cortisol (stress hormone) and adrenalin. These directly excite neurons and also increase blood sugar.

• Increasing blood sugar by drinking sugary drinks may help.

• Coffee and tea also result in increased arousal and may improve memory.
Practical applications

• Our sense of who we are depends on our memories of our life story, our relationships, and our goals.

• People who lose their ability to remember lose their sense of self.